

Applicant : Daniele Piomelli  
Serial No. : 09/864,920  
Filed : May 23, 2001  
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Attorney's Docket No. 07306-019001 / 2000-202-1

IN THE CLAIMS:

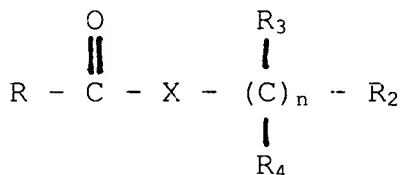
Please cancel claims 17-18 and 33-34, without prejudice.

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims

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1. (Currently Amended) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject in need of such treatment of a cannabinoid compound of formula I:



wherein X is N-R<sub>1</sub> or O;

R is a saturated or unsaturated, chiral or achiral, cyclic or acyclic, substituted or unsubstituted hydrocarbyl group,  
wherein the hydrocarbyl group has with 11 to 29 carbon atoms;

R<sub>1</sub>, R<sub>3</sub> and R<sub>4</sub> are selected independently from hydrogen, alkyl (C<sub>1-4</sub>), alkenyl (C<sub>2-4</sub>), alkynyl (C<sub>2-4</sub>), cycloalkyl (C<sub>3-6</sub>), or hydroxyalkyl group with from 2 to 4 carbon atoms;

R<sub>2</sub> is OH or O-CO-alkyl, where the alkyl group has from 1 to

4 carbon atoms; and

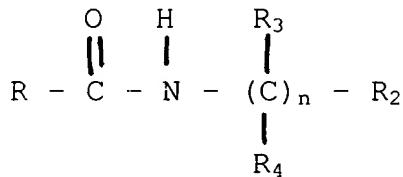
n is selected from 2 to 4.

2. (Currently Amended) The method of claim 1 wherein a methylene group in R is replaced with comprises 1 to 6 oxygen or sulfur atoms.

*Ay Cmt*  
3. (Original) The method of claim 1 wherein R2 is OH and X is N-H, and wherein they combine through the carbonyl group to form a heterocyclic ring structure.

4. (Currently Amended) The method of claim 3 wherein the heterocyclic ring structure is ~~selected from the group consisting of an oxazolidinone ring and a morpholine ring.~~

5. (Original) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject in need of such treatment of a cannabinoid compound of formula II:



wherein R is a saturated or unsaturated, substituted or unsubstituted hydrocarbyl group with from 15 to 29 carbon atoms;

R3 and R4 are selected independently from hydrogen, alkyl (C1-4), alkenyl (C2-4), alkynyl (C2-4), cycloalkyl (C3-6), or

hydroxyalkyl group with from 2 to 4 carbon atoms;

R2 is OH or O-CO-alkyl, where the alkyl group has from 1 to 4 carbon atoms;

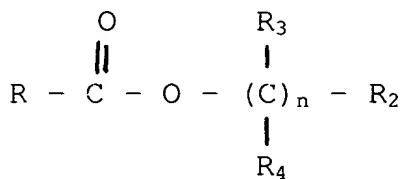
and

*A*  
*1*  
*Amend*  
*Cut*  
n is selected from 2 to 4.

6. (Currently Amended) The method of claim 5 wherein a methylene group in R comprises is replaced with 1 to 3 oxygen or sulfur atoms.

7. (Original) The method of claim 5 wherein R2 is OH and X is N-H, and wherein they combine to form a heterocyclic ring structure.

8. (Currently Amended) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject in need of such treatment of a cannabinoid compound of formula III:



wherein R is a saturated or unsaturated, substituted or unsubstituted hydrocarbyl group, wherein the hydrocarbyl group has with from 15 to 29 carbon atoms;

R3 and R4 are selected independently from hydrogen, alkyl (C1-4), alkenyl (C2-4), alkynyl (C2-4), cycloalkyl (C3-6), or

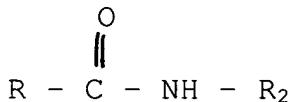
hydroxyalkyl group with from 2 to 4 carbon atoms;

R<sub>2</sub> is OH or O-CO-alkyl, where the alkyl group has from 1 to 4 carbon atoms; and

n is selected from 2 to 4.

*Ay  
Cmt*  
9. (Currently Amended) The method of claim 8 wherein a methylene group in R comprises is replaced with 1 to 3 oxygen atoms or sulfur atoms.

10. (Currently Amended) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject or the systemic administration to subject in need of such treatment of an inhibitor of endogenous cannabinoid inactivation of formula IV:



wherein R is a polyunsaturated, substituted or unsubstituted hydrocarbyl group, wherein the hydrocarbyl group has with from 18 to 22 carbon atoms;

R<sub>2</sub> is selected independently from substituted or unsubstituted cycloalkyl (C<sub>3</sub>-6) group and substituted or unsubstituted phenyl group.

11. (Original) The method of claim 10 wherein the phenyl group is selected from the group consisting of p-hydroxyphenyl and p-hydroxy-o-methyl-phenyl.

12. (Currently Amended) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject or the systemic administration to subject in need of such treatment of an inhibitor of endogenous cannabinoid inactivation of formula V:

*A-2 cont*  
 $R_1 - X - R_2$

wherein  $R_1$  is a saturated or polyunsaturated, substituted or unsubstituted hydrocarbyl group, wherein the hydrocarbyl group has with from 6 to 22 carbon atoms;

$X$  is  $-C=O$  or  $SO_2-$ ; and

$R_2$  is a halogen or a halogen-substituted methyl group.

13. (Original) The method of claim 1 wherein the cause of the cough can be persisting dry cough resulting from airway irritation and/or infection, angiotensin converting enzyme (ACE) inhibitors-induced cough, and cancer-induced cough.

14. (Original) The method of claim 10 wherein the method further comprises administration of a cannabinoid compound of formulae I, II, III, or any combination thereof.

15. (Original) The method of claim 11 wherein the method further comprises administration of a cannabinoid compound of formulae I, II, III, or any combination thereof.

16. (Original) A method of ameliorating cough comprising the local administration of a cannabinoid compound of formulae I, II, III, or any combination thereof, to the upper respiratory airways of patients in need of such treatment and whose vagal control of airway responsiveness is functional.

*A  
Box*  
17. (Canceled)

18. (Canceled)

19. (Original) The method of claim 1 wherein a cannabinoid of formulae I is selected from the group consisting of arachidonylethanolamide (anandamide), (R)-(+)-arachidonyl-1<sup>1</sup>-hydroxy-2<sup>1</sup>-propylamide, cis-7, 10, 13, 16-docosatetraenoylethanolamide, homo-delta-linoleyethanolamide, and N-propyl-arachidonylethanolamide.

20. (Original) The method of claim 10 wherein a cannabinoid inactivation inhibitor of formula IV is 4-(hydroxylphenyl)-arachidonylamide.

21. (Original) The method of claim 12 wherein a cannabinoid inactivation inhibitor of formula V is palmitylsulphonylfluoride or arachidonyltrifluoromethylketone.

22. (Original) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject in need of such treatment of a pharmaceutical composition

comprising a cannabinoid compound of formulae I, II, III, or any combination thereof.

23. (Original) The method of claim 22 wherein the method further comprises local or systemic administration of a pharmaceutical composition comprising a cannabinoid inactivation inhibitor of formulae IV, V, or any combination thereof.

*A/C  
Cont*  
24. (Original) The method of claim 23 wherein the pharmaceutical composition comprises compounds of formulae I, II, III, IV, V, or any combination thereof.

25. (Original) The method of claim 22, wherein the pharmaceutical composition is formulated for local delivery.

26. (Original) The method of claim 25 wherein the formulation for local delivery is by aerosol.

27. (Original) The method of claim 23 wherein the pharmaceutical composition is formulated for local delivery.

28. (Original) The method of claim 27 wherein the formulation for local delivery is by aerosol.

29. (Original) The method of claim 23 wherein the pharmaceutical composition is formulated for systemic delivery.

30. (Original) The method of claim 29 wherein the formulation for systemic delivery is by oral administration or intravenous

administration.

31. (Original) A pharmaceutical composition comprising a locally acting cannabinoid of formulae I, II, III, or any combination thereof, wherein the cannabinoid ameliorates cough and produces, at most, clinically insignificant side effects.

*Amx Cem*  
32. (Original) The pharmaceutical composition of claim 31 further comprising a pharmaceutically acceptable excipient.

33. (Canceled)

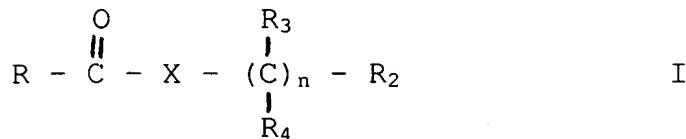
34. (Canceled)

Please add the following new claims:

--35. (New) The method of claim 1, wherein R2 is OH, and X is N-H and wherein they combine through an ethylene group to form a heterocyclic ring structure.

36. (New) The method of claim 35, wherein the heterocyclic ring structure is selected from morpholine or oxazepine.

37. (New) A method of ameliorating cough comprising the local administration to the upper respiratory airways of a subject in need of such treatment of a cannabinoid receptor agonist compound of Formula I



where R is a saturated or unsaturated, chiral or achiral, cyclic or acyclic, substituted or unsubstituted hydrocarbyl group with from 11 to 29 carbons and excluding aryl and methylene groups in said R optionally substituted with from 1 to 6 O or S atoms;

X is NR<sub>1</sub> or O;

R<sub>1</sub>, R<sub>3</sub> and R<sub>4</sub> are selected independently from hydrogen, alkyl (C<sub>1-4</sub>), alkenyl (C<sub>2-4</sub>), alkynyl (C<sub>2-4</sub>), cycloalkyl (C<sub>3-6</sub>), hydroxyalkyl group with from 2 to 4 carbon atoms and (CR<sub>3</sub>R<sub>4</sub>)<sub>n</sub> may be absent;

R<sub>2</sub> is selected from OH, O-CO-alkyl, substituted or unsubstituted cycloalkyl (C<sub>3-6</sub>) and aryl or aralkyl groups;

n is selected from 2 to 4.

38. (New) The method of claim 37 where X is NH and R<sub>2</sub> is OH then R<sub>2</sub> and X may combine through a carbonyl group or an ethylene group to form a heterocyclic ring structure.

39. (New) The method of claim 38 where the heterocyclic ring structure is selected from 2-oxazolidinone, morpholine or oxazepine.

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40. (New) The method of claim 37 where X is O and R2 is OH and O-CO-alkyl.

*Amt Cat*  
41. (New) The method of claim 37 where (CR<sub>3</sub>R<sub>4</sub>)<sub>n</sub> is absent and R2 is substituted or unsubstituted aryl or aralkyl groups.

42. (New) The method of claim 41 where the substituted aryl or aralkyl group is selected from p-hydroxyphenyl or p-hydroxy- $\alpha$ -methyl-phenyl.--